PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 211/90 | A1

(11) International Publication Number: **WO 99/52873**

(43) International Publication Date: 21 October 1999 (21.10.99)

(21) International Application Number: PCT/PL99/00011

(22) International Filing Date: 8 April 1999 (08.04.99)

(30) Priority Data:
P.325757 9 April 1998 (09.04.98) PL

(71) Applicant: ADAMED SP. Z O.O. [PL/PL]; Pieńków 149, PL–05–152 Czosnów k/Warszawy (PL).

(72) Inventors: WŁOSTOWSKI, Marek; ul. Siemiatycka 1/60, PL–01–312 Warszawa (PL). WIECZOREK, Maciej; ul. Garncarska 23, PL–27–400 Ostrowiec Świętokrzyski (PL).

(74) Agent: SITKOWSKA, Jadwiga; Patpol Ltd., ul. Nowoursynowska 162J, PL–02–766 Warszawa (PL).

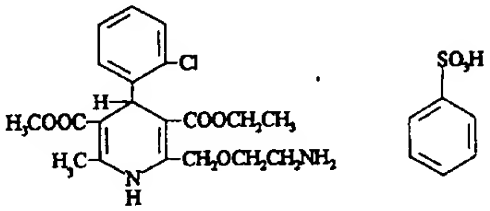
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A PROCESS FOR THE PREPARATION OF AMLODIPINE BENZENESULPHONATE



(57) Abstract

A process for the preparation of amlodipine benzenesulphonate is disclosed, wherein a salt of amlodipine with an inorganic or organic acid is reacted with alkali metal benzenesulphonate in an aqueous medium or in a mixture water–alcohol C_1–C_2. Amlodipine benzenesulphonate is used for the preparation of a medicament having calcium channel blocking activity, useful in the treatment of the coronary disease and arterial hypertension.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

A process for the preparation of amlodipine benzenesulphonate

The present invention relates to a process for the preparation of amlodipine benzenesulphonate, i.e. 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine monobenzenesulphonate of the formula I as presented on the annexed drawing.

Amlodipine is a modern medicament belonging to the group of calcium channel blockers. It has a significant selectivity against resistance arterioles and coronary arteries and specific pharmacokinetic properties: good bioavailability, long half-life, slow onset and decline of action onset as well as long-lasting pharmacological reaction, any substantial interactions with other medicaments being absent.

Due to these advantages amlodipine is utilized successfully in the treatment of arterial hypertension as a first choice therapeutic agent; it is also used successfully in the treatment of coronary disease, including Prinzmetal angina and other circulatory system diseases.

While amlodipine shows biological activity in its free base form, it is used in the pharmaceutical preparations as a salt with pharmacologically acceptable acids.

The European Patent Application EP 089,167 discloses a series of pharmaceutically acceptable amlodipine salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, maleate, tartrate, citrate and others. Maleate is indicated as the most preferred salt.

The European Patent Application EP 0244944 discloses the process for the preparation of amlodipine benzenesulphonate, which comprises treating amlodipine as a free base with benzenesulphonic acid or alternatively with benzenesulphonic acid ammonium salt in an inert organic solvent. In the examples of realisation (Examples I and V) industrial methyl alcohol is used as a solvent.

Amlodipine benzenesulphonate has been accepted for amlodipine administration both in the form of tablets and sterile aqueous solutions.

Amlodipine benzenesulphonate shows certain physical properties making it particularly destined for a pharmacologically acceptable amlodipine salt. It is much more stable than other salts both as a solid and a solution; it is relatively well soluble in water (4.6 mg/ml) but not hygroscopic. The pH of a saturated aqueous solution is about 6.6 being relatively close to the blood pH 7.4. Finally, due to its excellent mechanical properties can be easily compressed, forming tablets of a good quality without adhering to the punch of the tabletting machine, etc.

However, while amlodipine benzenesulphonate excellently meets the requirements for a good pharmaceutical material, the known process for preparing thereof has some disadvantages.

The process for the preparation of amlodipine benzenesulphonate according to EP 0244 944 comprises reacting free base of amlodipine with benzenesulphonic acid. The process is performed in an alcohol and thus may cause some fire hazard due to alcohol inflammability. The additional disadvantage is due to the fact that the reaction utilizes the free benzenesulphonic acid, which is a caustic, corroding and noxious substance. Additionally, due to its high hygroscopicity the acid requires the special safeguards during transport and handling and in practice is used in the form of dense oily material containing about 90% of acid and about 10% of water.

The alternative process also presents some hazards. Although the dangerous benzenesulphonic acid has been replaced with its ammonium salt, thus eliminating hazards and drawbacks connected with the use of free acid, the formation of amlodipine benzenesulphonate is accompanied, however, with the evolution of gaseous ammonia which is toxic and dangerous and has to be additionally absorbed and deactivated. Of course, the fire hazard connected with an inflammable alcohol is still present.

The above-discussed hazards and difficulties are eliminated by the process for the preparation of amlodipine benzenesulphonate of the present invention.

According to the process of the present invention, amlodipine salt with an inorganic or organic acid (with the

exception of salt with benzenesulphonic acid) is reacted with alkali metal benzenesulphonate in an aqueous medium or in a mixture water-alcohol C_1-C_2.

Preferably the amlodipine salt selected from acetate, formate, chloroacetate, hydrobromide, nitrate, hydrochloride, methanesulphonate is used. Especially preferred are hydrochloride, acetate or formate.

Alkali metal benzenesulphonate comprises lithium, sodium and potassium benzenesulphonate. Particularly preferred is sodium benzenesulphonate as an inexpensive, safe, stable and commercially available chemical product.

Preferred water-alcohol mixture is the mixture water-ethanol, comprising from 20 to 50% (v/v) of ethanol, especially 1:1 mixture.

The process of the invention may be realised by preparing a solution or a suspension of amlodipine salt in water or a water-alcohol mixture, and adding, preferably at 5-40°C with vigorous stirring, a solution of sodium benzenesulphonate in water in a stoichiometric amount or preferably at a molar ratio of sodium benzenesulphonate/amlodipine salt being 1:1.15. The mixture is stirred for about 10-60 minutes, optionally warmed to 40°C and then cooled to 10°C. The resulting precipitate of amlodipine benzenesulphonate is filtered off, washed twice with water and dried. If the salt separates as an oil, it is necessary to add some amlodipine benzenesulphonate crystals to speed the crystallization process. The product thus obtained contains no contaminants. Alternatively, the process can be performed by adding solid sodium benzenesulphonate to the amlodipine salt. The reverse order of reagents addition,

i.e. adding the amlodipine salt to the solution of sodium benzenesulphonate in water also results in a highly pure product.

The following non-limiting Examples are presented below to illustrate the invention:

Example 1

To the water (150 ml) amlodipine hydrochloride (71.5 g) was added and the mixture was stirred for 15 minutes at 20°C. The solution of sodium benzenesulphonate (33.3 g) in 200 ml of water was added portionwise during 10 minutes. A small amount of amlodipine benzenesulphonate crystals as seeds for crystallization was added and the mixture was stirred for 40 minutes. It was then cooled to 10°C and the resulting precipitate filtered off. The precipitate was washed with distilled water (3x 100 ml) and dried. 80.0 g of amlodipine benzenesulphonate was obtained, mp=201°C. Yield: 88%.

Example 2

To the solution of sodium benzenesulphonate (4 g) in water (20 ml) amlodipine formate (9.1 g) was added portionwise with stirring at 20°C. After addition had been completed, the mixture was stirred for 20 minutes, then cooled to 5°C and the product precipitate filtered off. The precipitate was washed with water (2 x 20 ml) and dried in vacuo. 18.8 g of amlodipine benzenesulphonate was obtained, mp=201°C. Yield: 90%.

Example 3

To the solution of amlodipine hydrobromide (9.6 g) in water (25 ml) sodium benzenesulphonate (4 g) was added portionwise with vigorous stirring. After addition had been

completed, the mixture was stirred for 20 minutes, then cooled to 5°C, and following the procedure of Example 2 11.6 g of amlodipine benzenesulphonate was obtained, mp=201°C.

Example 4

To the solution of sodium benzenesulphonate (4 g) in water (10 ml) amlodipine acetate (9.3 g) in 20 ml of the water-ethanol mixture (1:1) was added portionwise with stirring at 20°C. After addition had been completed, the mixture was stirred for 30 minutes, then cooled to 5°C, and several crystals of amlodipine benzenesulphonate and additionally 10 ml of water were added. Following the procedure of Example 2 amlodipine benzenesulphonate was obtained with the yield of 83%, mp=201°C.

Example 5

Starting from amlodipine chloroacetate (10.6 g) and sodium benzenesulphonate (4 g) and following the procedure of Example 1, amlodipine benzenesulphonate was obtained with 89% yield, mp=201°C.

Example 6

Starting from amlodipine methanesulphonate (10.6 g) and sodium benzenesulphonate (4 g) and following the procedure of Example 1, amlodipine benzenesulphonate was obtained with 81% yield, mp=201°C.

Example 6

Starting from amlodipine nitrate (9.4 g) and sodium benzenesulphonate (4 g) and following the procedure of Example 1, amlodipine benzenesulphonate was obtained with 83% yield, mp=201°C.

Claims

1. A process for the preparation of amlodipine benzenesulphonate of the Formula I, characterised in that a salt of amlodipine with an inorganic or organic acid is reacted with alkali metal benzenesulphonate in an aqueous medium or in a mixture water-alcohol C_1-C_2.

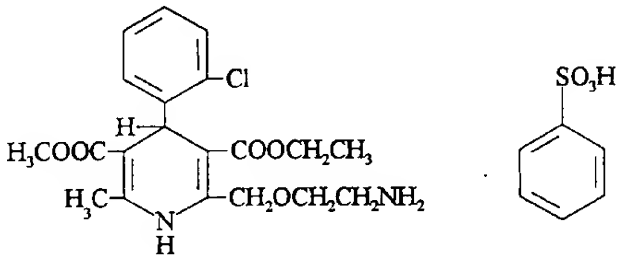
2. The process according to claim 1, characterised in that the salt of amlodipine is selected from acetate, formate, chloroacetate, hydrobromide, nitrate, hydrochloride or methanesulphonate, preferably hydrochloride.

3. The process according to any one of claims 1-2, characterised in that the alkali metal benzenesulphonate is sodium benzenesulphonate.

4. The process according to any one of claims 1-3, characterised in that the reaction is performed in the water-ethanol mixture containing from 20 to 50% of ethanol, especially 1:1 mixture.

5. The process according to any one of claims 1-4, characterised in that the reaction is performed in the aqueous medium.

6. The process according to claim any one of claims 1-5, characterised in that the reaction is performed at the temperature 5-40°C.



Formula I

INTERNATIONAL SEARCH REPORT

Interi ...nal Application No
PCT/PL 99/00011

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 244 944 A (PFIZER LTD) 11 November 1987 (1987-11-11) cited in the application the whole document; in partricular, page 9, lines 1-7	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 1999	13/08/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ional Application No
PCT/PL 99/00011

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0244944 A	11-11-1987	AP 50 A	16-09-1989
		AT 49752 T	15-02-1990
		AU 573123 B	26-05-1988
		AU 7103087 A	08-10-1987
		BE 1000130 A	12-04-1988
		BG 60698 B	29-12-1995
		CA 1321393 A	17-08-1993
		CN 1023800 B	16-02-1994
		CS 8702363 A	12-01-1989
		CS 9103539 A	15-04-1992
		CY 1669 A	14-05-1993
		DD 265142 A	22-02-1989
		DE 3710457 A	08-10-1987
		DK 170187 A	05-10-1987
		EG 18266 A	30-12-1992
		FI 871470 A,B,	05-10-1987
		FR 2596758 A	09-10-1987
		GB 2188630 A,B	07-10-1987
		GR 870525 A	12-08-1987
		GR 3000394 T	07-06-1991
		HK 76092 A	09-10-1992
		HR 950452 B	29-02-1996
		IE 59457 B	23-02-1994
		IN 168414 A	30-03-1991
		JP 1645822 C	13-03-1992
		JP 3007668 B	04-02-1991
		JP 62240660 A	21-10-1987
		KR 9506710 B	21-06-1995
		LU 86812 A	12-08-1987
		LV 5619 A	10-05-1994
		LV 5716 A	20-10-1995
		MX 5847 A	01-08-1993
		NL 8700791 A	02-11-1987
		PH 24348 A	13-06-1990
		PT 84611 A,B	01-05-1987
		SE 463457 B	26-11-1990
		SE 8701348 A	05-10-1987
		SI 8710580 A	31-12-1995
		SK 278435 B	07-05-1995
		SU 1498388 A	30-07-1989
		US 4879303 A	07-11-1989
		YU 58087 A	31-08-1988